REMARKS

Reconsideration of the above-identified application in view of the amendment above and the remarks below is respectfully requested.

Claim 2 has been canceled in this paper. Claims 1 and 3 have been amended in this paper. No new claims have been added in this paper. Therefore, claims 1 and 3 are pending and are under active consideration.

Claims 1-3 stand rejected under 35 U.S.C. 101 "because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966)."

Insofar as the subject rejection relates to claim 2, the rejection is moot in view of Applicant's cancellation herein of claim 2. Insofar as the subject rejection relates to claims 1 and 3, Applicant respectfully traverses the subject rejection.

Claims 1 and 3 have been re-written so that they are no longer directed at a use; instead, claims 1 and 3 are now directed at a compound preparation. As a result, the ground for the rejection is no longer applicable and should be withdrawn.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claims 1-3 stand rejected under 35 U.S.C. 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In support of the rejection, the Patent Office states the following:

> Claims 1-3 provide for the use of cinnarizine and dimenhydrinate or their physiologically compatible salts in combination for the treatment of vertigo of any genesis, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Insofar as the subject rejection relates to claim 2, the rejection is moot in view of Applicant's cancellation herein of claim 2. Insofar as the subject rejection relates to claims 1 and 3, Applicant respectfully traverses the subject rejection.

The subject rejection is predicated on claims 1 and 3 being "use" claims. However, as noted above, claims 1 and 3 are no longer "use" claims, but rather, are directed at compound preparations.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claims 1-3 stand rejected under 35 U.S.C. 102(b) "as being anticipated by the work of Halama." In support of the rejection, the Patent Offce states the following:

> Specifically, Halama teaches an Arlevert composition (i.e. combination of cinnazirine and dimenhydrinate) in the treatment of peripheral-vestibular and cerebral vertigo and the concomitant symptoms (see English abstract vs. instant claim 1). In particular, Halama teaches a control therapy where a tablet formulation of Arlevert was given and vertigo endpoints were evaluated using a cranial topography method (see page 1424, column 3 and table 3 vs. instant claim 2). It is further noted that the tablet Arlevert further composed of adjuvants and/or additives such as magnesium stearate, hypromellose, cellulose, etc....(German copy and see http://www.gelbe-liste.de). Accordingly, the teachings of Halama anticipate claims 1-3.

Insofar as the subject rejection relates to claim 2, the rejection is moot in view of Applicant's cancellation herein of claim 2. Insofar as the subject rejection relates to claims 1 and 3, Applicant respectfully traverses the subject rejection.

Claims 1 and 3 have been amended herein and now read as follows:

> 1. A compound preparation for dizziness comprising cinnarizine and dimenhydrinate or their physiologically compatible salts in combination for the treatment of vertigo of any genesis, wherein, in the combination, the dosage of cinnarizine and dimenhydrinate is reduced 2.5 times as compared to corresponding therapies with cinnarizine and dimenhydrinate individually.

> 3. A compound preparation for dizziness comprising cinnarizine and dimenhydrinate or their physiologically compatible salts in combination along with pharmaceutically compatible adjuvants and/or additives for the production of pharmaceuticals for the treatment of vertigo of any genesis, wherein, in the combination, the dosage of cinnarizine and dimenhydrinate is reduced 2.5 times as compared to corresponding therapies with cinnarizine and dimenhydrinate individually.

Support for the amendment to claims 1 and 3 may be found in the present specification, for example, at page 7, lines 11-16.

Claims 1 and 3 are neither anticipated by nor rendered obvious over Halama for at least the reason that Halama does not teach or suggest a compound preparation in which the dosage of cinnarizine and dimenhydrinate is reduced 2.5 times as compared to corresponding therapies with cinnarizine and dimenhydrinate individually. Instead, at best, Halama merely discloses that cinnarizine and dimenhydrinate may be used in combination to treat vertigo. Halama does not teach or suggest that there is a surprising, super additive synergism in the combination of these compounds nor does Halama disclose that the dosage must be 2.5 times lower to provide the super additive synergism. This surprising teaching was mentioned only for the first time in the present application. In this context, other surprising effects of the combination of the present invention are disclosed on page 7 of the present specification. The advantages are also disclosed in the examples discussed on

pages 7 to 11 of the present specification. These findings are surprising and would not have been expected by a person of ordinary skill in the art. In fact, these findings have recently been published by Applicant in numerous scientific publications. For example, the results of Study III on page 8 of the present specification have been published in Clinical Therapeutics, Vol. 26, No. 6, pp.866-877 (copy enclosed), and the results of Study IV on page 9 of the present specification have been published in Clin. Drug. Invest., 2005, 25(5):377-89 (copy enclosed).

Applicant respectfully submits that it was necessary to know the results of the examples given in the present specification in order to understand the full extent of the present invention. A person of ordinary skill in the art was not in a position to make the present invention based on the teachings of Halama nor was the present invention suggested in any way by Halama.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

In conclusion, it is respectfully submitted that the present application is now in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is

required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Kriegsman & Kriegsman

By: _____

Edward M. Kriegsman
Reg. No. 33,529
30 Turnpike Road, Suite 9
Southborough, MA 01772
(508) 481-3500

Dated: Apr 14, 2008

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on Apr 14, 2008.

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Edward M. Kriegsman

CLINICAL THERAPEUTICS®/VOL. 26, NO. 6, 2004

Treatment of Vertigo Due to Acute Unilateral Vestibular Loss with a Fixed Combination of Cinnarizine and Dimenhydrinate: A Double-Blind, Randomized, Parallel-Group Clinical Study

Arne W. Scholtz, MD, PhD,[1] Mario Schwarz, PhD,[2] Wolfgang Baumann, PhD,[2] Dieter Kleinfeldt, MD,[3] and Heinz-Joachim Scholtz, MD, PhD[3]

[1]*Department of Otorhinolaryngology, University of Innsbruck, Austria,* [2]*Medical Science Department, Hennig Arzneimittel, Floersheim am Main, and* [3]*Department of Otorhinolaryngology, University of Rostock, Germany*

ABSTRACT

Background: Acute unilateral vestibular loss is a balance disorder that is accompanied by vertigo symptoms and concomitant vegetative symptoms, including nausea and vomiting. Patients are frequently confined to bed rest but may continue to experience vertigo symptoms. A well-established antivertiginous therapy consisting of cinnarizine and dimenhydrinate at low doses may offer rapid relief of acute vertigo symptoms due to acute vestibular loss, without inhibiting physiological compensation processes.

Objective: The purpose of this study was to compare the clinical efficacy and tolerability of a fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg versus monotherapy with its respective components in the treatment of acute vertigo symptoms due to acute unilateral vestibular loss.

Methods: In this prospective, single-center, randomized, double-blind, parallel-group clinical study, 50 patients with acute vestibular vertigo were randomly assigned to receive 4 weeks of treatment (1 tablet 3 times daily) with a fixed combination of 20 mg cinnarizine and 40 mg dimenhydrinate, 20 mg cinnarizine alone, or 40 mg dimenhydrinate alone. All patients received a 15% mannitol infusion as standard therapy during the first 6 days of treatment. Efficacy was determined by the patients' assessments of vertigo symptoms after 1 and 4 weeks of treatment using a verbal rating scale (vertigo score) and by vestibulo-ocular and vestibulospinal tests. The primary efficacy criterion was defined as the relief of vertigo symptoms after 1 week of treatment.

Results: After 1 week of treatment, the fixed combination was significantly more effective than 20 mg cinnarizine ($P < 0.001$) and 40 mg dimenhydrinate ($P < 0.01$). After 4 weeks, the fixed combination was still significantly more effective than cinnarizine in reducing vertigo symptoms ($P < 0.01$) and significantly more effective than dimenhydrinate in improving the patients' balance while standing ($P < 0.05$). The tolerability of the fixed combination was rated good or very good by 100% of the patients (cinnarizine alone, 82.4%; dimenhydrinate alone, 94.4%). No serious adverse events occurred. Four patients in the fixed combination and the cinnarizine groups, and 6 patients in the dimenhydrinate group reported nonserious adverse events.

Conclusions: The results of this study suggest a distinct benefit in using a fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg versus the respective monotherapies in this population of patients with acute vestibular vertigo. (*Clin Ther.* 2004;26:866–877) Copyright © 2004 Excerpta Medica, Inc.

Key words: vertigo, nystagmus, cinnarizine, dimenhydrinate, combination.

Accepted for publication March 30, 2004.

0149-2918/04/$19.00

INTRODUCTION

The maintenance of balance in humans requires an active sensorimotor control system for keeping the body inside its limits of stability.[1] This complex physical task is based on finely tuned brain processing of sensory inputs provided by the vestibular, visual, and proprioceptive systems as well as the cognitive system. Data mismatch induced by unusual and therefore unadapted stimulation of the intact sensory systems, or pathological dysfunction of any of these afferent components or of the brain centers integrating these signals may lead to the symptom of vertigo.[2,3] Many diseases, such as coronary heart disease, hypertension, or diabetes may be involved in the pathogenesis of unsystematic balance disorders; however, systematic vertigo is caused by disorders of the vestibular system.[4]

Chronic vertigo is more common than vertigo caused by acute vestibular loss. Yet, acute unilateral vestibular loss can have considerable impact,[1,5] because it immediately leads to rotatory vertigo attacks accompanied by spontaneous horizontal-rotatory nystagmus, postural imbalance, nausea, vomiting, and other vegetative symptoms.[2] In addition, sensorineural hearing loss, tinnitus, and aural fullness may occur. Patients presenting with acute vestibular failure are confined to bed rest for up to 1 week.[2] Symptoms caused by acute unilateral vestibular loss are progressively compensated by physiologic adaptation of the brain to the modified situation.[5]

In general, the long-term prognosis is good with respect to patients' ability to manage their daily activities. However, activity restrictions for the patient may persist, and chronification of vertigo symptoms may occur, especially in elderly patients.[6] The prevalence of acute as well as chronified vertigo increases with age, and imposes great limitations on a patient's activities of daily living.[7,8] Patients with vertigo are prone to frequent falls with corresponding injuries.[9] Patients' insecurity while standing and loss of self-confidence as a result of vertigo may further lead to their chronic immobilization. The social consequences of vertigo, together with the increasing age of the population, underscore the importance of developing effective antivertiginous therapies for both individual care and pharmacoeconomic reasons.[10]

Due to the complexity and diversity of the pathogenic mechanisms underlying vertigo, pharmacologic as well as physical therapy approaches have been used in its treatment. Drugs used in the treatment of vertigo include antihistamines, calcium antagonists, histamine analogs (eg, betahistine derivatives), diuretics, neuroleptics and other psychotherapeutic drugs, corticosteroids, and hemorheologic agents.[11] Two commonly used agents are cinnarizine, a selective calcium-channel blocker, and dimenhydrinate, an H_1 antihistamine; these agents have been used successfully for many years in the treatment of vertigo.[11] Cinnarizine acts as an inhibitor of vestibular excitability by suppressing calcium influx into vestibular sensory cells. Through its specific inhibition of calcium entry into arterial smooth muscle cells, cinnarizine improves cerebral and cochlear perfusion.[12–14] Dimenhydrinate exerts antivertiginous and antiemetic effects via its regulatory potential, affecting the vestibular nuclei and closely associated vegetative centers in the brainstem.[15,16]

For more than 20 years, a fixed combination of these 2 drugs has been successfully used for the treatment of vertigo of peripheral, central, or combined peripheral/central origin. The rationale for creating a fixed, low-dose combination of the 2 drugs is based on the dual mode of action of the individual components. Since its introduction in the market, a total of 17 controlled clinical studies have been conducted on the cinnarizine-dimenhydrinate combination. The proven efficacy and good tolerability of the fixed combination versus various standard therapies in the treatment of chronified vertigo have been well established in 7 randomized, double-blind, placebo- and/or reference-controlled clinical studies of patients with various types of vertigo.[17–19] To our knowledge, the study presented here is the first to evaluate this drug combination in patients with vertigo due to acute vestibular disorders. Acute vestibular loss is usually treated with several different drugs. The ideal medication should, however, suppress the sensation of vertigo, help restore normal balance, and prevent vomiting, and should not impede the normal process of recovery from the vestibular lesion.[5] The present study assessed the efficacy and tolerability of the fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg in comparison with the respective monotherapies cinnarizine 20 mg and dimenhydrinate 40 mg in the treatment of vertigo due to acute unilateral vestibular loss.

PATIENTS AND METHODS

Study Population

Adult inpatients at the ENT Clinic at the University of Rostock who had vertigo due to acute unilateral vestibular failure or unilateral vestibular neuropathy were eligible to participate in the study. The diagnoses were confirmed by examination of gaze-evoked, positional, and caloric nystagmus (monitoring of side differences by means of photoelectronystagmography [PENG] and electronystagmography [ENG]). Exclusion criteria were in accordance with the fixed combination's contraindications and included convulsive seizures, suspected compressive intracranial processes, angle-closure glaucoma, prostate adenoma, Parkinson's disease, asthma, gastrointestinal ulcer, acute intoxication, severe renal insufficiency, epilepsy, and alcohol abuse. Women who were pregnant, lactating, or not practicing contraception during the study period were also excluded. Use of antivertiginous drugs other than the study medication was not permitted during the study.

Protocol

This randomized, double-blind, reference-controlled, single-center, parallel-group Phase III clinical study was conducted at the ENT Clinic, University of Rostock, Germany. It was performed in accordance with the principles of Good Clinical Practice and the recommendations of the Declaration of Helsinki (1989 revision). The study was approved by the appropriate local ethics committee. All patients were informed about the study in detail (orally and in writing) and gave their written informed consent before enrollment. Patients were randomized to 4 weeks of treatment (1 tablet 3 times daily) with the fixed combination of 20 mg cinnarizine and 40 mg dimenhydrinate, cinnarizine 20 mg per tablet, or dimenhydrinate 40 mg per tablet. All patients also received a 15% mannitol infusion as standard therapy during the first 6 days (**Figure 1**). The patients stayed in the hospital during the first week of the study period and were subsequently dismissed to continue their respective drug therapies at home. Patients underwent an entry examination (before the start of treatment), an intermediate examination (after 7 ± 2 days), and a final examination (after 28 ± 2 days). At each visit, vertigo symptoms, vegetative symptoms concomitant to vertigo, and other symptoms concomitant to vertigo were recorded.

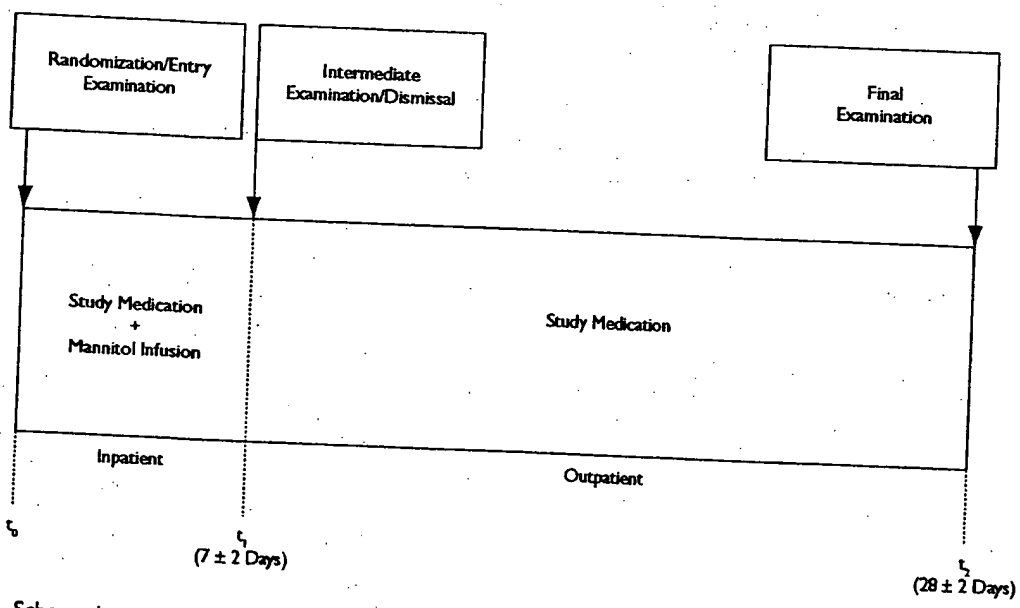

Figure 1. Schematic representation of the investigational plan. Study medication: fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg per tablet (1 tablet 3 times daily); or cinnarizine, 20 mg per tablet (1 tablet 3 times daily); or dimenhydrinate, 40 mg per tablet (1 tablet 3 times daily).

Vestibulo-ocular tests (nystagmus tests) and vestibulospinal tests (Romberg's test) were performed at each visit. Hearing was tested using pure tone audiometry at the entry and final examinations. Global efficacy and tolerability were judged by both the investigator and patient after 4 weeks of treatment. Adverse events were recorded at the intermediate and final examinations, based on direct questioning or medical findings. Furthermore, the patients were advised to contact the investigator if adverse events occurred during the course of the study. Compliance with treatment was assessed by counting the tablets returned by the patients at the end of the treatment period. During hospitalization, medication intake was controlled by the nursing staff (mouth check). Study medication was manufactured by Hennig Arzneimittel (Floersheim am Main, Germany) according to Good Manufacturing Practice. Test medication and reference medication were indistinguishable with respect to appearance, taste, weight, shape, and packaging.

Evaluation of Efficacy

Primary Efficacy Criterion

The primary criterion of efficacy was the relief of vertigo symptoms and vertigo intensity following trigger factors (ie, movements leading to vertigo symptoms) after 1 week of treatment. The patients evaluated the intensity of their vertigo symptoms using a verbal rating scale (VRS) in which 0 = no symptom, 1 = mild, 2 = moderate, and 3 = severe. Symptoms assessed at each patient visit included unsteadiness (dystasia and walking unsureness), staggering, rotary sensation, tendency to fall, lift sensation, and swaying, as well as the intensity of vertigo following 6 specific trigger factors—change of position, bowing, getting up, walking, head movements, and eye movements. A mean vertigo score, S_M, was calculated from the VRS-based quantified intensities of the aforementioned vertigo symptoms plus the quantified intensities of the vertigo following the 6 trigger factors; thus, S_M represents a parameter for the global evaluation of vertigo severity. The reduction in S_M after 1 week of treatment was the primary study outcome measure.

Secondary Efficacy Criteria

Secondary criteria of efficacy included the relief of vertigo symptoms and vertigo intensity following trigger factors after 4 weeks of treatment; relief of vegetative and other symptoms concomitant to vertigo; vestibulospinal, vestibulo-ocular, and audiometric assessments; and global efficacy.

Vegetative and Other Symptoms Concomitant to Vertigo

Vegetative symptoms concomitant to vertigo (ie, nausea, vomiting, sweating, tachycardia, and headache) were recorded by the patients. Based on the value of each of these symptoms, a mean vegetative score (V_M) was established and was analyzed the same way as S_M. In addition, other symptoms concomitant to vertigo (ie, pressure sensation in the ear, tinnitus, impaired hearing, impaired vision, ocular symptoms, and bulbar symptoms) were reported.

Vestibulospinal Tests

Vestibulospinal movement patterns of patients while performing Romberg's (standing) test were recorded using computer-aided posturography. Body sway was evaluated by means of the displacements of the gravity center as reflected by the posturography sway areas on the x and y axes. Evaluation of Romberg's test was based on the Romberg Index, which represents the ratio of the measured areas of total sway with eyes open and with eyes closed.

Vestibulo-ocular Tests

Gaze-evoked and positional nystagmus were analyzed using Frenzel's glasses. Occurrence of gaze-evoked nystagmus was examined at the main glance directions, followed by assessment of positional nystagmus by monitoring nystagmus reactions at the dorsal position with head to the right, head to the left, and sitting up.

The caloric nystagmus test was performed to determine the side of the vestibular lesion and to identify disorders of the labyrinth and the vestibular nerve. Caloric testing was done by irrigation of either ear with cool (30°C) and warm (44°C) water (100 mL for 30 seconds). Using PENG and ENG, nystagmus slow-phase velocity (SPV) as well as frequency (beats per 30 seconds) were determined during the middle 30-second period at maximum reaction. To determine the presence of a unilateral weakness, the response strength from each side was compared using Jongkees's formula.

Global Efficacy

At the end of the final visit, patients and the investigator were asked to evaluate the global efficacy of the treatment based on a VRS in which 1 = very much improved, 2 = much improved, 3 = slightly improved, and 4 = not improved.

Tolerability

The tolerability assessment was based on reports of adverse events occurring after drug intake. The events were either reported spontaneously by the patients, observed by the investigator, or reported by the patients in response to general questioning by the investigator. Adverse reactions were recorded in detail at each follow-up visit and classified according to the COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) body system. At the end of the final visit, patients and the investigator rated the global tolerability of the drugs based on a verbal rating scale, where 1 = very good, 2 = good, 3 = moderate, and 4 = poor.

Statistical Analysis

The statistical analysis was performed on the per-protocol population. All enrolled patients completed the study according to protocol. The primary efficacy variable was the change in S_M from baseline. The confirmatory analysis was performed in the hierarchical order (first) 1 week and (second) 4 weeks after the start of treatment. The primary efficacy variable showed a low approximation to normal distribution. Therefore, treatment groups were compared nonparametrically (Kruskal-Wallis test) at a global significance level of 0.05. In accordance with the Bonferroni correction, simultaneous comparisons between the treatment groups were performed at a significance level of $\alpha = 0.025$. Due to nonhomogeneous initial distributions, the variable S_M was subjected to analysis of covariance (ANCOVA) with adjustment of means at the end of the study using the initial values as covariates. In addition, 2-sided 95% CIs for changes from baseline between the treatment groups were determined. The changes in single vertigo symptoms were analyzed by means of exact contingency table tests. Similarly, an exploratory analysis was performed on additional secondary variables to compare changes between treatment groups during the course of the study.

RESULTS

Demographic Characteristics of Study Population

A total of 50 patients were randomized into 3 treatment groups (fixed combination, 15 patients; cinnarizine 20 mg, 17 patients; and dimenhydrinate 40 mg, 18 patients). All patients completed the study according to protocol. Treatment groups were comparable with respect to demographic characteristics, except for weight; there was a slight imbalance at the 20% significance level due to a lower minimum weight in the dimenhydrinate group ($P < 0.2$) (**Table I**). The

Table I. Demographic and clinical characteristics of the study population (N = 50).

	Fixed Combination (n = 15)	Cinnarizine (n = 17)	Dimenhydrinate (n = 18)
Sex, no. (%)			
Male	6 (40)	10 (59)	7 (39)
Female	9 (60)	7 (41)	11 (61)
Age, mean ± SD (range), y	51.47 ± 9.79 (37–66)	51.35 ± 10.76 (33–68)	53.83 ± 14.32 (31–77)
Body weight, mean ± SD (range), kg	79.20 ± 15.16 (60–117)	77.41 ± 10.20 (63–91)	72.83 ± 16.19† (52–118)
Height, mean ± SD (range), cm	168.40 ± 8.81 (155–186)	169.35 ± 7.70 (154–183)	166.94 ± 8.07 (152–185)
Body mass index,* mean ± SD (range), kg/m²	27.73 ± 3.17 (22.31–33.82)	27.00 ± 3.18 (20.31–32.66)	25.96 ± 4.23† (19.10–34.48)

*Body mass index = body weight /(height in m)².
†Inhomogeneous at the 20% level with respect to the fixed combination.

study population included 27 women and 23 men. The mean age was 52.3 years and the mean body mass index was 26.9 kg/m^2. All patients had a confirmed diagnosis of acute vestibular neuropathy. A total of 28 patients reported concomitant diseases, with cardiovascular disease being the most frequently reported (~40%). Compliance was nearly 100%, and no differences between the treatment groups with respect to compliance were observed.

Clinical Efficacy

Relief of Vertigo Symptoms and Vertigo Following Trigger Factors

The fixed combination was significantly more effective than both cinnarizine 20 mg alone ($P < 0.01$) and dimenhydrinate 40 mg alone ($P < 0.01$) in reducing S_M after 1 week (**Table II**). The baseline S_M values of the fixed combination group were homogeneous with respect to the baseline scores of the reference medication cinnarizine (Kruskal-Wallis test, $P = 0.272$), but showed a slight imbalance at the 20% significance level with respect to dimenhydrinate (Kruskal-Wallis test, $P = 0.157$). Correction for initial nonhomogeneity by ANCOVA resulted in an even more pronounced difference in efficacy of the fixed combination compared with cinnarizine after 1 week of treatment ($P < 0.001$). All 3 treatments led to a strong improvement in S_M throughout the 4-week treatment period compared with the respective baseline values. However, after 4 weeks of treatment, the fixed combination resulted in significantly greater relief of vertigo symptoms than the comparator cinnarizine 20 mg without ($P < 0.05$) or with adjustment by ANCOVA ($P < 0.01$). Changes in S_M (before and after adjustment by ANCOVA) with the respective 95% CIs are shown in Table II, and 95% CIs for differences between treatment groups are presented in **Table III**.

Vestibulospinal Tests

At the entry examination, 27 of the 50 patients, equally distributed among all treatment groups, were unable to perform Romberg's test because of severe vertigo symptoms. Thus, no initial values were available for these patients. For the remaining 23 patients, the Romberg Index had homogeneous mean values between 1.00 and 1.12 in all treatment groups. Within the first week of treatment, the Romberg Index decreased markedly followed by a further, less pronounced decline during the subsequent 3 weeks in all treatment groups. The fixed combination group showed the largest reductions both after 1 and 4 weeks of treatment; however, the differences were statistically significant only compared with the dimenhydrinate group after 4 weeks ($P < 0.05$, **Table IV**). One week after the onset of treatment, the 27 patients who initially had been incapable of performing Romberg's test were able to do so. For the evaluation of Romberg Index changes for all patients during the course of the study, a hypothetical maximum index of 2.0 was set as the initial value for these 27 patients, taking into account the severity of the disease in these patients and the index values observed in the first examination

Table II. Changes in the mean vertigo score (S_M) during the course of the study.

	After 1 Week			After 4 Weeks		
	Mean Reduction	95% CI	P^*	Mean Reduction	95% CI	P^*
Fixed combination (n = 15)						
Mean change ± SD	2.09 ± 0.41	1.87–2.32		2.39 ± 0.33	2.21–2.58	
Adjusted mean†	2.12			2.41		
Cinnarizine (n = 17)						
Mean change ± SD	1.57 ± 0.46	1.33–1.80	0.003	2.11 ± 0.36	1.92–2.29	0.037
Adjusted mean†	1.56		<0.001	2.10		0.005
Dimenhydrinate (n = 18)						
Mean change ± SD	1.65 ± 0.33	1.49–1.82	0.002	2.15 ± 0.33	1.98–2.31	0.035
Adjusted mean†	1.64		0.003	2.14		0.060

*Versus fixed combination, Kruskal-Wallis test.
†Calculated after adjustment for nonhomogeneous initial distribution by analysis of covariance.

Table III. Least-squares means and 95% CIs for differences in mean vertigo score (S_M) between the fixed combination and comparative study drugs.

	Least-squares Mean*	95% CI
Fixed combination vs cinnarizine	0.36	0.16–0.56
Fixed combination vs dimenhydrinate	0.29	0.12–0.47

*Mean difference adjusted for baseline values (analysis of covariance) of baseline minus 1 week.

in the remaining study population (maximum = 1.91). The resulting initial values in the complete patient population (n = 50) showed a homogeneous distribution among the treatment groups with mean values between 1.49 and 1.61. Analyses that included the 27 patients who had not performed the initial Romberg test revealed the same results as analyses with patients tested at all 3 visits (n = 50).

Vegetative Symptoms Concomitant to Vertigo

The baseline V_M of the fixed combination group was homogeneous compared with the V_M baseline values of the reference medications cinnarizine and dimenhydrinate. After 1 week of treatment, the V_M of all 3 groups decreased to ~10% of the initial value, reflecting a marked relief of the patients' vegetative symptoms. During the next 3 weeks, vegetative symptoms subsided almost completely (**Table V**). No significant differences between the effects of the 3 medications were observed.

Other Symptoms Concomitant to Vertigo

The complaints of tinnitus, impaired hearing, and pressure sensation in the ear were homogeneously distributed among treatment groups at baseline. These symptoms were reported by 1 to 3 patients per treatment group except for tinnitus in the cinnarizine group, which was reported by 6 patients at the entry examination. Due to the low frequency of occurrence, an analysis of changes with treatment was not appropriate.

Vestibulo-ocular Tests

Initially, the entire patient population presented with a pronounced spontaneous nystagmus (not shown). Similar to the mean vertigo score S_M, spontaneous nystagmus was markedly reduced from 100% to 80% after 1 week and to 28% at the end of 4 weeks' treatment. No significant differences were observed between treatment groups. Positional nystagmus could not be assessed at the first and intermediate examinations in 100% and 72% of the patients, respectively, due to superimposition by spontaneous nystagmus. Analysis of the available data showed no statistically significant differences between treatment groups (not shown). Evaluation of caloric nystagmus was based on SPV measured by means of PENG and ENG. According to the characteristics of the underlying disease, the patients initially presented with hyporeflexia or areflexia on the affected side. The corresponding SPV values ranged from 0 to 11.4 deg/s. The treatment groups were homogeneous with respect to the initial distribution of mean SPV values at either the affected or unaffected side. As shown in **Figure 2**, caloric nystagmus at the affected side markedly improved with treatment. The initial, very low SPV increased during treatment, resulting in means of 5.98 ± 4.13 deg/s after 1 week and 9.28 ± 6.33 deg/s after 4 weeks of treatment, with no statistically significant differences between the treatment

Table IV. Changes in Romberg Index* during the course of the study.

	After 1 Week		After 4 Weeks	
	Mean Reduction ± SD	p†	Mean Reduction ± SD	p†
Fixed combination (n = 15)	0.90 ± 0.52		1.25 ± 0.59	
Cinnarizine (n = 17)	0.71 ± 0.43	0.406	0.96 ± 0.56	0.059
Dimenhydrinate (n = 18)	0.72 ± 0.54	0.347	1.01 ± 0.59	0.043

*With estimated maximal Romberg Index of 2 for missing values at baseline.
†Versus fixed combination, Kruskal-Wallis test.

Table V. Changes in mean vegetative score (V_M) during the course of the study.

	After 1 Week		After 4 Weeks	
	Mean Reduction ± SD	P^*	Mean Reduction ± SD	P^*
Fixed combination (n = 15)	1.68 ± 0.41		1.77 ± 0.45	
Cinnarizine (n = 17)	1.53 ± 0.51	0.447	1.71 ± 0.58	0.747
Dimenhydrinate (n = 18)	1.60 ± 0.41	0.585	1.78 ± 0.49	0.870

*Versus fixed combination, Kruskal-Wallis test.

groups. The increase in mean SPV, indicating the recovery of the nystagmus reaction, was significant both after 1 and 4 weeks ($P < 0.001$ in all groups). On the other hand, SPV values at the contralateral side remained unaffected during the course of treatment.

Global Efficacy

The global efficacy judgments by the investigator and the patients were very similar, and corresponded with the marked improvements in vertigo symptoms during the course of therapy. In both cases, the statistical analysis confirmed the significantly greater efficacy of the fixed combination with respect to cinnarizine and the absence of a significant difference in efficacy compared with dimenhydrinate (**Table VI**).

Tolerability

All 3 treatments proved to be well tolerated. No serious adverse events (AEs) were reported during the study. The rate of nonserious AEs was consistent across treatment groups; all AEs were of mild to moderate intensity and had subsided by the end of treatment. None of the patients withdrew due to AEs, and all patients completed the study according to protocol within 28 ± 2 days. Overall, 14 of 50 patients (28.0%) reported AEs. The rate of AEs was 26.7% in

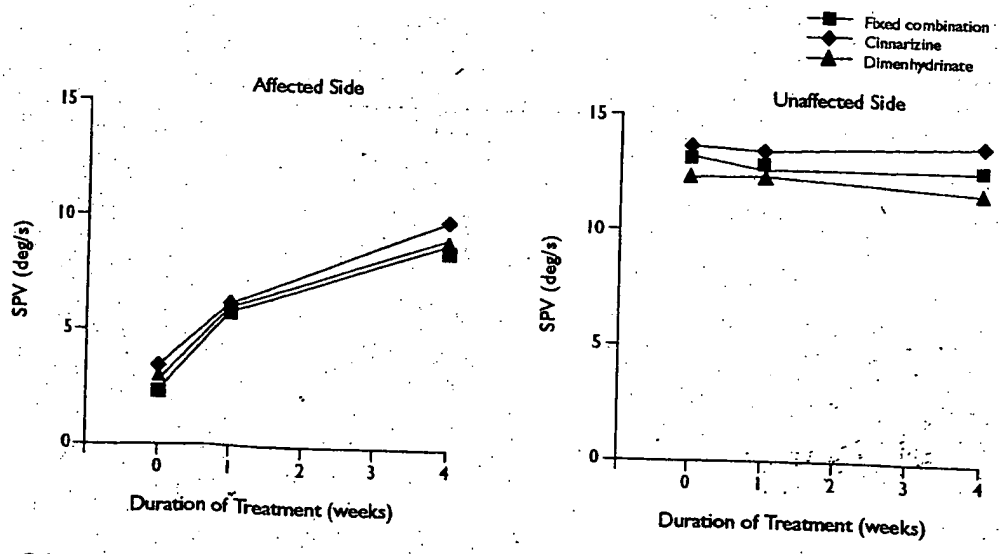

Figure 2. Caloric nystagmus on the affected and unaffected sides of vestibular loss. Evaluation was based on the velocity of the slow phase of nystagmus (slow-phase velocity [SPV] in degrees per second), which was determined automatically by a calculation program that received the data from the recording apparatus.

Table VI. Global efficacy as judged by the investigator and patients after 4 weeks of therapy.

	No. (%) of Patients			
	Very Much Improved	Much Improved	Slightly Improved	P
Investigator's judgment				
Fixed combination	6/15 (40.0)	7/15 (46.7)	2/15 (13.3)	
Cinnarizine	–	14/17 (82.4)	3/17 (17.6)	0.010
Dimenhydrinate	7/18 (38.9)	9/18 (50.0)	2/18 (11.1)	1.000
Patients' judgment				
Fixed combination	9/15 (60.0)	5/15 (33.3)	1/15 (6.7)	
Cinnarizine	1/17 (5.9)	11/17 (64.7)	5/17 (29.4)	0.001
Dimenhydrinate	8/18 (44.4)	8/18 (44.4)	2/18 (11.1)	0.686

the fixed combination group (4/15 patients, 5 AEs), 23.5% in the cinnarizine group (4/17 patients, 6 AEs), and 33.3% in the dimenhydrinate group (6/18 patients, 8 AEs), with no significant differences between groups (**Table VII**). The most frequent AE across the study population was fatigue, followed by headache. Since these symptoms are frequently caused by the underlying disease, it remains unclear whether they represented adverse drug reactions or symptoms of acute vestibular loss. The tolerability of the treatments is underscored by the patients' judgments of treatment tolerability at the end of the study. In the fixed combination group, 100% of patients rated the tolerability of treatment as very good or good; the corresponding rates in the cinnarizine and dimenhydrinate groups were 82.4% and 94.4%, respectively (**Table VIII**).

DISCUSSION

Patients with acute vestibular loss are incapable of maintaining their balance and experience intense vertigo and strong vegetative symptoms, including nausea and vomiting. Due to the severity of symptoms, patients are generally confined to bed rest for diagnosis and treatment. The standard therapy consists primarily of bed rest and infusion with drugs such as

Table VII. Adverse events in the randomized population (N = 50).

Adverse Event (COSTART Code)	Body System (COSTART)	Fixed Combination (n = 15)	Cinnarizine (P vs fixed combination) (n = 17)	Dimenhydrinate (P vs fixed combination) (n = 18)	Total (%)
Tiredness*	Nervous system	3	1 (0.32)	4 (1.0)	8 (16.0)
Dryness of mouth	Digestive system	–	1 (1.0)	1 (1.0)	2 (4.0)
Abdominal pressure sensation	Digestive system	–	–	1 (1.0)	1 (2.0)
Headache	Body	2	3 (1.0)	2 (1.0)	7 (14.0)
Tachycardia	Cardiovascular system	–	1 (1.0)	–	1 (2.0)
Total		5	6	8	19
No. (%) of patients reporting adverse event		4/15 (26.7)	4/17 (23.5)	6/18 (33.3)	14/50 (28.0)

COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms.
*Tiredness has to be coded as "somnolence" according to the COSTART code.

Table VIII. Judgment of tolerability by investigator and patients after 4 weeks of treatment.

	No. (%) of Patients			
	Very Good	Good	Moderate	P
Investigator's judgment				
Fixed combination	12/15 (80.0)	3/15 (20.0)	–	
Cinnarizine	9/17 (52.9)	7/17 (41.2)	1/17 (5.9)	0.191
Dimenhydrinate	11/18 (61.1)	6/18 (33.3)	1/18 (5.6)	0.558
Patient's judgment				
Fixed combination	11/15 (73.3)	4/15 (26.7)	–	
Cinnarizine	7/17 (41.2)	7/17 (41.2)	3/17 (17.6)	0.120
Dimenhydrinate	11/18 (61.1)	6/18 (33.3)	1/18 (5.6)	0.843

pentoxyphylline, cortisone, or mannitol. However, patients often continue to experience strong vertigo symptoms during compensation and need additional symptomatic relief, especially within the first week after vestibular failure. Therefore, the simultaneous administration of antivertiginous medication is often useful. In the present study, the fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg provided this additional benefit for patients with acute vestibular loss. The combination was significantly more effective than the monotherapy components in reducing vertigo symptoms within the first week of treatment ($P < 0.01$). Although the major benefit of this combination therapy is the rapid (within the first week) improvement of vertigo, long-term therapeutic effects are also evident. After 4 weeks of treatment, vertigo symptoms as well as vegetative symptoms concomitant to vertigo resolved almost completely across the entire study population, with no major differences between the treatment groups. However, the fixed combination was still significantly more effective than cinnarizine in reducing vertigo symptoms ($P < 0.01$). In addition, Romberg's test confirmed the therapeutic advantage of the fixed combination compared to the reference therapies after 4 weeks, demonstrating a statistically significant difference compared with dimenhydrinate ($P < 0.05$). The greater efficacy of the fixed combination compared with its single active components might be explained pharmacologically by the dual mechanism of action of the combination. Cinnarizine, a calcium-channel blocker,[20] improves cochlear circulation and decreases labyrinth excitability at peripheral vestibular sites.[11–14] Dimenhydrinate is a centrally acting H_1 antihistamine. The combination, therefore, provides antivertiginous activity at both peripheral and central sites, resulting in a synergistic effect. The effects of the fixed combination and the single-agent components were accompanied by the effects of the standard infusion therapy—reconstitutive processes and central compensation. The partial recovery of the caloric nystagmus at the affected side as well as the gradual decrease in spontaneous nystagmus (both showing no significant differences between treatment groups) may be explained by regenerative processes. Additional studies that include a placebo control are required to determine the contributions of the fixed combination or its components to these processes. With respect to compensation, 2 recent studies demonstrated that the combination product only marginally affects vigilance, suggesting that central compensation processes are not suppressed.[21,22] The rate of AEs in the fixed combination group was similar to those found in the reference groups, and all patients rated the tolerability of the fixed combination as good or very good. Thus, the combination of cinnarizine 20 mg and dimenhydrinate 40 mg has the favorable tolerability of the low-dose single agents, but has greater clinical efficacy. Since no placebo group was included in this study, it remains unclear whether the reported AEs were drug-specific. Nevertheless, the benefit/risk ratio of the fixed combination exceeded that of both reference medications. The results in patients with acute vestibular vertigo are consistent with those from previous studies, which demonstrated the antivertiginous efficacy and good tolerability of the fixed combi-

nation in the treatment of patients with chronified vertigo of peripheral vestibular, central vestibular, or combined peripheral/central vestibular origin, as well as Ménière's disease.[17–19,23] The knowledge gained from these investigations, together with the results presented herein, underscore the therapeutic advantage of the fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg in the treatment of acute or chronified vertigo due to vestibular failure.

CONCLUSIONS

In this study, the fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg proved to be significantly more effective than the respective monotherapies in reducing vertigo due to acute vestibular loss within the first week of treatment while supporting compensation processes. Hence, this fixed combination represents not only a well-established treatment for chronic vestibular vertigo, but also an effective treatment option for acute vestibular vertigo.

ACKNOWLEDGMENTS

This study was supported by Hennig Arzneimittel, Floersheim am Main, Germany. The authors thank Dr. Andreas Iwanowitsch for statistical analysis.

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Address correspondence to: Mario Schwarz, PhD, Medical Science Department, Hennig Arzneimittel, Liebigstr 1-2, D-65439 Floersheim am Main, Germany. E-mail: schwarz@hennig-arn.de

ORIGINAL RESEARCH ARTICLE

Clin Drug Invest 2005; 25 (6): 377-389
1173-2563/05/0006-0377/$34.95/0

Efficacy and Tolerability of a Fixed Combination of Cinnarizine and Dimenhydrinate versus Betahistine in the Treatment of Otogenic Vertigo

A Double-Blind, Randomised Clinical Study

Zdenek Cirek,[1] *Mario Schwarz*,[2] *Wolfgang Baumann*[2] and *Miroslav Novotny*[3]

1 ENT Clinic Pilsen of Charles University, Prague, Czech Republic
2 Hennig Arzneimittel, Floersheim/Main, Germany
3 ENT Clinic Sv. Anna Hospital, Masaryk University, Brno, Czech Republic

Abstract

Introduction: Peripheral vestibular disorders frequently lead to the manifestation of symptoms of vertigo. The objective of this study was to compare the efficacy and tolerability of a fixed combination of cinnarizine 20mg and dimenhydrinate 40mg per tablet with betahistine (betahistine dimesylate) 12mg per tablet in the treatment of patients with otogenic vertigo.

Patients and methods: Sixty-one patients with vertigo due to peripheral vestibular disorders (otogenic vertigo) participated in this prospective, double-blind, comparative, single-centre study. Patients were randomly allocated to treatment with betahistine 12mg or the fixed combination of cinnarizine 20mg and dimenhydrinate 40mg, both treatments given three times daily for 4 weeks. Efficacy was determined by patients' assessments of vertigo symptoms after 1 and 4 weeks of treatment using a visual analogue scale to determine a 'mean vertigo score'.

Results: Treatment with the fixed combination led to significantly greater improvements in mean vertigo scores compared with the reference therapy betahistine. This was evident as early as 1 week after the onset of treatment ($p = 0.002$). Over 4 weeks of therapy, the fixed combination decreased the intensity of vertigo symptoms about 2-fold compared with betahistine ($p = 0.001$). Furthermore, reductions in symptoms typically associated with vertigo were more pronounced ($p = 0.009$) in the fixed-combination group compared with the betahistine group after 4 weeks of treatment. No serious adverse events were reported in either treatment group. Tolerability of the fixed combination was judged as 'very good' by 97% (betahistine 90%) and as 'good' by 3% (betahistine 10%) of patients.

Conclusion: The fixed combination of cinnarizine and dimenhydrinate was shown to be an effective and very well tolerated treatment option for patients with otogenic vertigo. It proved to be statistically more efficient in reducing vertigo than the widely used betahistine. Therefore, the fixed combination of cinnarizine and dimenhydrinate may be considered a first-line treatment option for the treatment of otogenic vertigo.

Maintenance of balance is essential for the management of daily activities. This complex physical function depends on finely tuned brain processing of sensory inputs provided by the vestibular, visual and proprioceptive systems as well as by the cognitive system. Data mismatch induced by unusual and therefore unadapted stimulation of the intact sensory systems, or pathological dysfunction of any of these afferent components or of the brain centres integrating these signals, give rise to the condition 'vertigo'.[1,2] Therefore, vertigo not only represents a cardinal symptom for vestibular disorders, but is furthermore associated with a wide spectrum of diseases. Vertigo may also appear in association with various organic diseases or may have a psychogenic origin.[3,4]

In practice, the pathogenesis of most cases of vertigo involves disorders of the vestibular system.[3,4] The vestibular system is generally divided into peripheral and central compartments. The peripheral vestibular system comprises the semicircular canals, the otoliths, the hair cells and the vestibular nerve up to the root entry zone in the brainstem. The central vestibular system, on the other hand, is composed of the vestibular nuclei, the oculomotor nuclei, the vestibuloocular reflex tracts, the cerebellum, the brainstem reticular formation, the area postrema, and other components.[5] Vertigo can occur as a consequence of peripheral vestibular disorders or central nervous system diseases; in many cases, combined forms of vertigo of central and peripheral origin are observed. Associated symptoms differ depending on the origin of vertigo and thus provide diagnostic information to guide systematic investigation of the underlying cause. Nevertheless, establishing a diagnosis is often difficult because of the complexity and diversity of the underlying pathogenic mechanisms and the patient's subjective perception of vertigo symptoms.[2,6]

Common peripheral vestibular diseases include vestibular neuritis and vestibular neuropathy, bacterial and viral labyrinthitis, benign paroxysmal positional vertigo (BPPV), Ménière's disease, labyrinth or vestibular nerve trauma, otosyphilis, tumours, otosclerosis, perilymphatic fistula, autoimmune inner ear disease, vasculitides and ototoxicity caused by drugs or toxic chemicals.[7,8] Typical manifestations of peripheral vestibular disorders are vertigo (predominantly rotating) accompanied by nausea, vomiting and other autonomous symptoms, sensorineural hearing loss, tinnitus and aural fullness.[7,8] Vertigo imposes great limitations on patients' ability to meet their daily responsibilities, which results in a self-perceived decrease in quality of life.[9,10] Vertiginous patients are also prone to frequent falls and thus injuries.[11] Eventually, their insecurity about standing and loss of self-confidence may lead to immobilisation. The social consequences of vertigo and the increasing age of the population underline the importance of developing efficient antivertiginous therapies for both individual care and pharmacoeconomic reasons.[12]

Because of the complexity and diversity of the pathogenic mechanisms underlying vertigo, drugs of various pharmacological classes have been used to treat this condition. These include calcium channel antagonists, antihistamines, the histamine-like

drug betahistine, diuretics, antipsychotics and other psychotherapeutic drugs, corticosteroids and haemorrheological agents.[13] In this study we report on the efficacy and tolerability of a fixed combination consisting of the calcium channel antagonist cinnarizine (20mg per tablet) and the antihistamine dimenhydrinate (40mg per tablet) [Arlevert®, Hennig Arzneimittel (Floersheim/Main, Germany)[1] compared with betahistine, which is widely accepted as a standard medication for the treatment of peripheral vestibular vertigo.[14] This fixed combination of cinnarizine and dimenhydrinate has been used successfully in Germany for >20 years for the treatment of vertigo of various origins, including peripheral, central or combined peripheral/central types of vertigo. The rationale for the use of the fixed combination is based on its dual mode of action: because of its calcium channel antagonistic properties, cinnarizine rapidly regulates calcium influx into the vestibular cells of the labyrinth and, in the long term, improves cerebral circulation,[15-18] while dimenhydrinate primarily exerts a regulatory effect on the vestibular nuclei and adjacent vegetative centres in the brainstem.[19,20]

Since its introduction to the market, a total of 17 controlled clinical studies with various objectives have been conducted using this combination product. The superior efficacy and favourable tolerability of the fixed combination compared with various standard treatments has been demonstrated in seven individual, randomised, double-blind, placebo- and/or reference-controlled clinical studies in patients with diverse types of vertigo as well as Ménière's disease.[21-25]

The present study assesses the efficacy and tolerability of the fixed combination of cinnarizine and dimenhydrinate in the treatment of patients with vertigo exclusively due to peripheral vestibular disorders of otogenic origin. The combination drug was compared with the standard treatment betahistine. In Germany, the latter agent is licensed for use in 'vertigo conditions in the context of Ménière-like symptoms', and is widely used for the treatment and prophylaxis of peripheral vertigo, including vertigo attacks associated with Ménière's disease.

Patients and Methods

Patient Population

Study participants were outpatients of either sex, aged >30 years, with otogenic vertigo. Specific inclusion criteria were intensities of one or more vertigo symptoms rated by the patient as at least 'medium' on a graded visual analogue scale (VAS) ranging from 'no symptoms' to 'very strong symptoms' (see *Evaluation of Efficacy*). In addition, patients were required to present with abnormal vestibulospinal movement patterns in Unterberger's test (craniocorpography [CCG]) to be eligible.

Patients who had Ménière's disease were excluded from participation in the study because treatment of this disease consists of long-term prophylactic therapy extending for a much longer period of time than the 4-week duration of the current study. Patients with BPPV, vertigo due to unsolved organic primary disease (i.e. non-vestibular origin) or bilateral caloric inexcitability (areflexia) were also excluded. Furthermore, pregnant or lactating women, and women not using a safe method of contraception during the study were excluded. There were no restrictions on duration of disease, pre-treatment, and concomitant diseases, except those known to be contraindications to the medications used. With regard to concomitant medication, participants taking antivertiginous or cerebrovascularly active drugs were required to discontinue such therapies 1 week prior to the start of treatment (1-week washout phase). The use of further drugs that could have

1 The use of trade names is for product identification purposes only and does not imply endorsement.

interfered with the study medication was prohibited throughout the study.

Protocol

This clinical study was designed as a randomised, double-blind, reference-controlled, single-centre, parallel-group phase III study. It was performed in accordance with the principles of Good Clinical Practice and the recommendations of the Declaration of Helsinki in its current version. Study documents were reviewed and approved by the appropriate local ethics committee and the National Institute of Pharmaceuticals. Prior to the study, all patients were informed about the study in detail (orally and in writing) and provided written informed consent before enrolment in the study.

Patients were randomly assigned to 4 weeks of treatment with either the fixed combination of cinnarizine 20mg and dimenhydrinate 40mg (3 × 1 tablet daily), or the reference medication betahistine (betahistine dimesylate 12mg per tablet, 3 × 1 tablet daily). Randomisation was based on a computer-generated sequence that ensured equal distribution of patients among the different treatment groups according to US FDA standards. Randomisation lists remained with the sponsor and were not accessible to the investigators. To ensure that appropriate measures could be taken in cases of medical emergency and maintain the integrity of the double-blind design for unaffected patients, the investigators received sealed envelopes that contained the decoding information for each patient separately.

Study medication was manufactured by Hennig Arzneimittel (Floersheim/Main, Germany) according to Good Manufacturing Practice. To guarantee double-blind conditions, the test and reference medications were indistinguishable with respect to appearance, taste, weight, shape and packaging. The quality of the batches used in this study was guaranteed by the corresponding certificates of analysis.

Patients were subjected to an entry examination (before the start of treatment), an intermediate examination (after 7 ± 2 days), and a final examination (after 28 ± 2 days). At each visit, vertigo symptoms, symptoms concomitant with vertigo and any other symptoms were recorded; vestibulospinal tests (Unterberger's and Romberg's tests) [see *Diagnostic Procedures*] and vestibulo-ocular tests (spontaneous, positional and caloric nystagmus) were also performed. In addition, hearing was tested by means of threshold audiometry during the entry and final examinations. Adverse events were registered at follow-up and final examinations; these events were identified by direct questioning or as medical findings. However, patients were also advised to contact the investigator in case of adverse events during the course of the study. Overall efficacy and tolerability were judged by both the investigator and patients at the intermediate and final visits. Compliance with treatment was assessed by counting the tablets returned by patients at the end of the treatment period.

Evaluation of Efficacy

Vertigo Symptoms

The efficacy evaluation was based on patients' assessments of the intensity of vertigo symptoms. Reduction of vertigo symptom intensity is the most direct and important parameter for the evaluation of patients' vertigo complaints during the course of the antivertigo treatment.[3] As the primary efficacy variable, change in the 'mean vertigo score' (VS_M) was used as a global parameter for vertigo intensity. VS_M was defined as the mean of the intensities of six vertigo symptoms and vertigo in consequence of six trigger factors, as evaluated by the patients using a VAS. The symptoms assessed at each of the patients' visits were the vertigo symptoms unsteadiness, staggering, rotary sensation, tendency to fall, lift sensation and blackout; vertigo following the six trigger factors – change of position, bowing, getting

up, head movements, riding by car/train and eye movements – was also documented.

Patients evaluated their vertigo symptom intensities according to a standardised questionnaire by means of a graded VAS, where: 0 = no symptoms, 1 = moderate symptoms, 2 = medium symptoms, 3 = strong symptoms, and 4 = very strong symptoms. Treatment efficacy was analysed by comparing changes from baseline VS_M associated with use of either medication. To ensure the reliability of the mean VS_M score, which is composed of the above-mentioned 12 individual symptom scores, the consistency of the individual scores with respect to VS_M was evaluated by calculating Cronbach's alpha coefficients. Secondary variables of efficacy were vegetative and concomitant symptoms of vertigo, outcomes of vestibulospinal and vestibulo-ocular tests, audiometry and assessment of global efficacy.

Vegetative and Concomitant Symptoms of Vertigo

Patients rated the intensities of vegetative symptoms – i.e. nausea, vomiting, sweating and tachycardia – and concomitant symptoms of vertigo such as tinnitus and impaired hearing. Based on the scores of each symptom, a 'mean concomitant symptom score' (CSS_M) was established.

Evaluation of Overall Efficacy

At the end of the intermediate and final visits, patients and investigator were asked to evaluate the overall efficacy of treatments with respect to vertigo symptoms, vegetative symptoms and concomitant symptoms based on a graded verbal rating scale: 1 = very much improved, 2 = much improved, 3 = slightly improved, 4 = not improved, and 5 = deteriorated.

Diagnostic Procedures

Vestibulospinal Tests

Unterberger's and Romberg's tests were performed and registered using CCG[3] at entry (before therapy), at the intermediate visit (after 1 week) and at the final visit (after 4 weeks of therapy). Briefly, CCG is a diagnostic procedure by which characteristic light patterns corresponding to the head-body sway of the patient are recorded. From these patterns, the following parameters can be determined – Unterberger's test: deviation of the patient to the right or to the left (angular deviation), body spin, staggering of the patient's head and body (lateral sway) and longitudinal deviation; Romberg's test: anterior-posterior shift and lateral shift.

Vestibulo-Ocular Tests

Spontaneous and positional nystagmus were analysed using Frenzel's glasses. Gaze nystagmus was examined under the following conditions: glance to the right, to the left, straight ahead and upwards. Positional nystagmus was determined by monitoring the eyes for nystagmus in the following positions: supine with head downward, sitting-up, dorsal with head to the right and to the left, respectively.

The bithermal caloric test was performed to localise the side of a vestibular lesion and to identify disorders of the labyrinth and the vestibular nerve. Caloric testing was conducted by directly irrigating the ear canal and ear drum with cool (30°C) and warm (44°C) water (20mL for 30 seconds). Nystagmus frequency (beats/30 sec) was determined by means of electronystagmography (ENG) during the central 30-second period at maximum reaction. For the determination of a unilateral weakness, the response strength of each side was compared using Jongkees' formula.

Evaluation of Tolerability

Assessment of tolerability was based on reports of adverse events that occurred after drug intake. Adverse events were reported spontaneously by patients, observed by the investigator, or reported by patients in response to general questioning by the investigator. Adverse reactions were registered in

detail at each visit and classified according to the WHO code. Blood pressure was measured using standard procedures at each examination. At the end of the follow-up and final visits, patients and investigator rated the global tolerability of treatment on a four-level rating scale graded: 1 = very good, 2 = good, 3 = moderate, and 4 = poor.

Statistical Analysis

Sample size calculation was based on the t-test model, assuming a difference between the test medications in the reduction of VS_M of d = 0.25 with an estimated standard deviation of s = 0.33. With α = 0.05 and a type II error of β = 0.1, a sample size of 30 patients per group was required. Statistical analysis was performed on the original data on the basis of the intent-to-treat population, which was identical to the per-protocol population.

Confirmatory analysis of the primary efficacy variable VS_M was based on change in this variable from baseline in hierarchical order: (1) 4 weeks after start of treatment, and (2) 1 week after start of treatment. Differences between test medications were analysed by Student's t-test or, in case of insufficient normal approximation, non-parametrically using the Wilcoxon-Mann-Whitney U test. The level of significance was set as α = 0.05. Categorical variables were compared by Fisher's Exact test. In addition, two-sided CIs at the 95% level for changes from baseline between the two treatment groups were determined.

Table I. Selected demographic and other baseline characteristics

	Fixed combination (n = 30)	Betahistine (n = 31)	p-Value (Kruskal-Wallis statistics)
Sex			
male	13	11	0.605[a]
female	17	20	
Age (y)[b]			
mean	49.60 ± 12.31	48.58 ± 11.76	0.812[a]
range	(31–77)	(30–72)	
Height (cm)[b]			
mean	168.50 ± 7.14	169.74 ± 7.83	0.483
range	(157.00–183.00)	(153.00–183.00)	
Weight (kg)[b]			
mean	76.73 ± 13.21	75.29 ± 11.82	0.644
range	(52.00–108.00)	(52.00–98.00)	
Body mass index (kg/m^2)[b]			
mean	26.99 ± 4.16	26.06 ± 3.34	0.411
range	(19.13–36.79)	(19.84–33.98)	
Duration of vertigo (mo)[b]			
mean	30.37 ± 45.89	29.42 ± 45.23	0.789
range	(0.50–204.00)	(0.50–180.00)	
No. of patients with premedication	19	20	
No. of patients exposed to:			
noise	4	5	
vibrations	1	3	
No. of patients with concomitant diseases	3	4	

a Exceeding probability (p-value) of Fisher's Exact test.

b Results are given as mean ± SD with minimum and maximum values in parentheses.

Table II. Reduction in mean vertigo score (VS_M) after treatment with fixed combination (cinnarizine and dimenhydrinate) or betahistine for 1 and 4 weeks (intent-to-treat, per-protocol)

Time-point	Decrease in VS_M from baseline[a]				p-Value[b]
	fixed combination (n = 30)		betahistine (n = 29)		
	mean ± SD	95% CI[c]	mean ± SD	95% CI	
After 1 week	0.65 ± 0.42	0.49, 0.81	0.31 ± 0.38	0.16; 0.45	0.002
After 4 weeks	1.07 ± 0.58	0.85, 1.29	0.51 ± 0.56	0.30, 0.73	0.001

a Changes from baseline are calculated 'pre- minus post-', i.e. positive values correspond to improvements of symptoms.

b Exceeding probability of Kruskal-Wallis statistics.

c Confidence interval.

Secondary variables were analysed in an explorative manner only. For quantitative data, Student's t-test or, in case of insufficient normal approximation, the Wilcoxon-Mann-Whitney U test was used. For categorical data, Fisher's Exact test was applied. Homogeneity of the initial distribution of the primary and secondary variables as well as demographic baseline distribution was tested using the above-mentioned methods; in case of insufficient homogeneity of the initial distributions, an analysis of covariance (ANCOVA) was performed with adjustment of the mean values at the end of the study using the initial values as covariates.

Comparability of demographic and clinical variables between treatment groups was assessed using the chi-squared (χ^2) test in case of categorical data. For quantitative data, analysis of variance (ANOVA) or, in case of insufficient normal approximation, the Kruskal-Wallis test, was used. In case of insufficient homogeneity of the initial distributions, ANCOVA was performed with adjustment of means at the end of the study using the initial values as covariates.

Results

Disposition of Patients and Demographic Characteristics

Sixty-one Caucasian outpatients were enrolled in the study and randomised to receive either the fixed combination (n = 30) or betahistine (n = 31). Table I shows the demographic and other baseline attributes of all patients. There were no statistically significant differences with respect to any demographic characteristics among the treatment groups. The duration of illness was consistent between the therapy groups. The two groups were comparable with regard to pretreatment and frequency of concomitant diseases.

All patients were diagnosed with vertigo of peripheral vestibular origin (otogenic vertigo). Aetiologies included otosclerotic inner ear disease (n = 9), uncompensated vestibular neuritis (n = 7), status post-stapedectomy (n = 1), status post-myringoplasty (n = 1), cochleovestibular disorders (e.g. vertebrobasilar insufficiencies, immune-mediated,

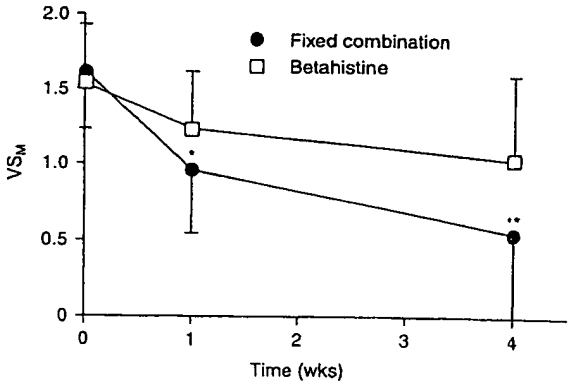

Fig. 1. Change in mean vertigo score (VS_M) [primary efficacy variable] during the course of the study. VS_M was defined as the mean of the intensities of six vertigo symptoms and vertigo as a result of six trigger factors, as evaluated by patients using a visual analogue scale. * p = 0.002; ** p = 0.001 (exceeding the probability of Kruskal-Wallis statistics). **Fixed combination** = fixed combination of cinnarizine 20mg and dimenhydrinate 40mg.

Table III. Effects of treatment with fixed combination (cinnarizine and dimenhydrinate) or betahistine on single vertigo symptoms and on vertigo intensity following single trigger factors after 4 weeks (intent-to-treat, per-protocol)

Single vertigo symptoms and trigger factors	Fixed combination vs betahistine p-value[a]
Unsteadiness	0.009
Staggering	0.003
Rotary sensation	0.046
Tendency to fall	0.006/0.021[b]
Lift sensation	0.444/0.632[b]
Blackout	0.763
Changing position	0.004
Bowing	<0.001
Getting up	0.001
Moving the head (twist, inclination)	0.006/0.029[b]
Riding by car/train	0.141
Moving eyes	0.256

a Exceeding probability of Kruskal-Wallis statistics.

b Adjusted means (adjusted inhomogeneously distributed initial scores).

metabolic or endocrine dysfunctions of inner ear structures; n = 20), and degeneration processes in the inner ear due to disorders of vascular origin, e.g. atherosclerosis (n = 23).

Two patients in the betahistine group terminated the study prematurely for unknown reasons after the entry examination and were lost to follow-up. All 59 patients who completed the study fulfilled the criteria for per-protocol analysis and were included in the efficacy analysis.

Clinical Efficacy

Vertigo Symptoms

The primary study outcome measure was the reduction of VS_M over the course of the 4-week treatment period. The fixed combination was superior to the reference therapy betahistine in improving vertigo symptoms. Significantly greater reductions in VS_M were observed in the fixed-combination group, becoming evident 1 week after the start of treatment ($p = 0.002$). Over the 4-week study period, fixed-combination therapy decreased VS_M about 2-fold compared with betahistine ($p = 0.001$).

Baseline VS_M scores in the fixed-combination group were similar to those of the reference medication betahistine group (Dunnett's test, $p = 0.337$). Before the start of therapy, mean VS_M values were 1.61 ± 0.39 and 1.54 ± 0.37 in the fixed-combination and betahistine groups, respectively. Both treatments improved VS_M throughout the 4-week treatment period with respect to baseline values. After 4 weeks of treatment, 9 of 30 patients (36.67%) in the fixed-combination group had no vertigo complaints (vertigo score = 0), whereas only 2 of 29 patients (6.9%) in the betahistine group were without complaints. Changes in VS_M during the 4-week treatment period are summarised in table II and figure 1.

The fixed combination proved to be superior to betahistine not only in reducing vertigo symptoms represented by VS_M, but also in reducing four of six single vertigo symptoms and in reducing vertigo intensity following four of six trigger factors (see table III). Thus, the observed VS_M results were consistent with those found in the analysis of single symptoms, which was confirmed by calculating Cronbach's alpha coefficients for each individual symptom. Alpha values were consistent, with indi-

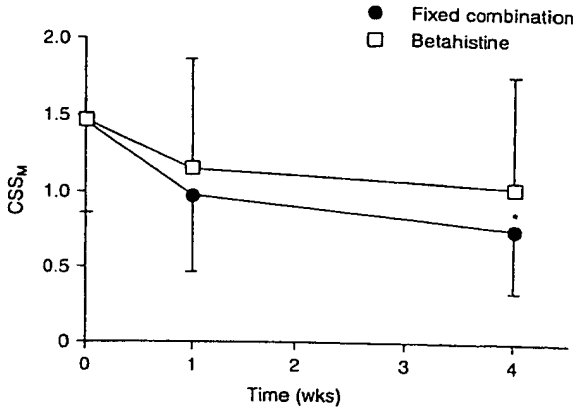

Fig. 2. Change in mean concomitant symptom score (CSS_M) during the course of the study. These scores were obtained from patients' judgements of the intensities of the six symptoms nausea, vomiting, sweating, tachycardia, tinnitus and impaired hearing. * $p = 0.009$ (exceeding probability of Kruskal-Wallis statistics). Fixed combination = fixed combination of cinnarizine 20mg and dimenhydrinate 40mg.

Table IV. Change in mean concomitant symptom score (CSS_M) after treatment with fixed combination (cinnarizine and dimenhydrinate) or betahistine for 1 and 4 weeks (intent-to-treat, per-protocol)

Time-point	CSS_M – change from baseline (mean ± SD)		p-Value[a]
	fixed combination (n = 30)	betahistine (n = 29)	
After 1 week of therapy	−0.50 ± 0.48	−0.32 ± 0.39	0.111
After 4 weeks of therapy	−0.72 ± 0.49	−0.44 ± 0.50	0.009

a Exceeding probability of Kruskal-Wallis statistics.

vidual variables ranging from 0.81 to 0.86 (total 0.84) after 1 week and from 0.90 to 0.93 (total 0.92) after 4 weeks.

Vegetative and Concomitant Symptoms of Vertigo

CSS_M baseline scores for the fixed combination and betahistine groups were comparable (Dunnett's test). The fixed combination was significantly superior ($p = 0.009$) to betahistine in reducing CSS_M over the course of the 4-week treatment period (figure 2, table IV). In particular, the vegetative symptoms nausea and vomiting, which frequently accompany vertigo, subsided almost completely after 4 weeks of treatment with the fixed combination. The significant superiority of the fixed combination in comparison with betahistine was statistically confirmed for the vegetative symptom nausea after 4 weeks of therapy ($p = 0.02$).

Vestibulospinal Tests

The mean values of angular deviation, lateral sway and longitudinal deviation decreased during the course of the study, with no significant differences between the two treatments (data not shown). The values of the parameter 'anterior/posterior shift' did not show any changes during therapy in either treatment group (data not shown). Values of the parameter 'lateral shift' progressively decreased relative to baseline with therapy in both treatment groups (data not shown).

Vestibulo-Ocular Tests

Five patients presented with spontaneous nystagmus (three in the fixed-combination group, two in the betahistine group). One patient from the betahistine group showed a positional nystagmus at the left and right positions. Except for one case, the symptoms persisted throughout the study.

Both therapies affected caloric-induced nystagmus reactions. Under all four irrigation conditions, the initially relatively high frequencies of induced nystagmus decreased during the course of therapy. No statistically significant differences could be detected between the treatment groups during therapy (data not shown).

Table V. Patients' assessment of efficacy after treatment with fixed combination (cinnarizine and dimenhydrinate) or betahistine for 1 and 4 weeks (intent-to-treat, per-protocol)[a]

Time-point	Fixed combination (n = 30) [no. (%)]	Betahistine (n = 29) [no. (%)]
1 week[b]	26 (86.7) much + slightly improved	15 (51.7) much + slightly improved
	4 (13.3) not improved	14 (48.3) not improved
4 weeks	26 (86.7) very much + much + slightly improved	17 (58.6) very much + much + slightly improved
	3 (10.0) not improved	9 (31.0) not improved
	1 (3.3) deteriorated	3 (10.3) deteriorated

a Patients and investigator rated the treatment efficacy on a 5-point scale. There were no relevant differences between ratings of patients and investigator.

b The differences in the ratings after 1 week were statistically significant ($p = 0.006$). After 4 weeks, differences were not statistically significant.

Investigator's and Patients' Assessment of Overall Efficacy

Both patients and investigator rated the overall efficacy of the fixed combination significantly higher than that of the reference treatment after 1 week (patients: $p = 0.006$; investigator: $p = 0.008$). After 4 weeks, the efficacy of the fixed combination was still rated higher than the efficacy of betahistine by patients and investigator, but the differences were no longer statistically significant (table V).

Tolerability

Both treatments were well tolerated. No serious adverse events were reported in the course of the study. Two patients from the betahistine group terminated the study prematurely for unknown reasons and were lost to follow-up. In addition, two patients who received betahistine reported non-serious adverse events (headache: one patient; abdominal pain: one patient). All patients and the investigator rated the tolerability of both medications as either 'very good' or 'good' after 1 and 4 weeks (table VI).

Systolic and diastolic blood pressures were similar at baseline in the two study groups. Neither the fixed combination nor betahistine caused any statistically significant or clinically relevant changes in blood pressure (figure 3).

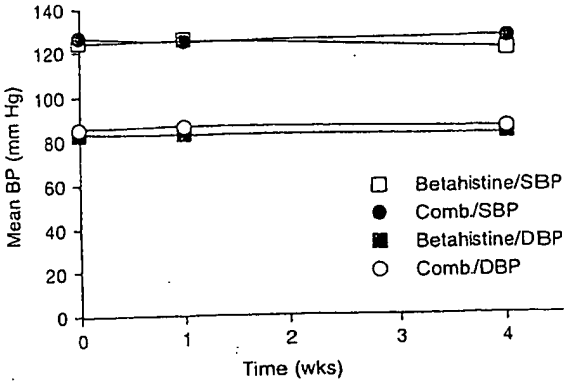

Fig. 3. Mean blood pressure (BP) during the course of the study. Systolic (SBP) and diastolic (DBP) blood pressures were measured at each examination visit according to the Riva Rocci method. Values for SBP ranged from 90 to 180mm Hg; the mean values were 124.50 ± 18.86mm Hg in the betahistine group and 126.83 ± 20.23mm Hg in the fixed-combination (fixed combination of cinnarizine 20mg and dimenhydrinate 40mg) group. Baseline DBP values varied from 60 to 110mm Hg; the mean values were 83.17 ± 10.04mm Hg in the betahistine group and 85.33 ± 11.21mm Hg in the fixed-combination group. **Comb.** = fixed combination.

Discussion

Evaluating treatment success in patients with vertigo is difficult because of the complexity of this disease and the lack of unambiguous apparatus-based parameters. Primarily, the crucial criterion for evaluating therapy success is the subjective severity of vertigo symptoms tormenting the patient. Nevertheless, apparatus-based methods are useful for corroborating the results of the vertigo diagnosis. In addition to a thorough evaluation of case history, such tools are helpful for establishing the correct diagnosis for the individual patient. In the present study, both subjective symptom-based and apparatus-based measures have been used to measure the effectiveness of therapy. Since VS_M represents a parameter for the global evaluation of vertigo severity and characterises the intensity of the individual patient's vertigo sensations, independently of the type of vertigo, it serves as an effective measure of progress with treatment for both test medications.

The two active components of the fixed combination – cinnarizine (20mg per tablet) and dimenhydrinate (40mg per tablet) – have distinct pharmacological properties that complement one another synergistically. While cinnarizine acts predominantly on the peripheral vestibular labyrinth by affecting local calcium ion flux,[15-17] dimenhydrinate is pri-

Table VI. Patients' assessment of tolerability after treatment with fixed combination (cinnarizine and dimenhydrinate) or betahistine for 4 weeks (intent-to-treat, per-protocol)[a]

Rating	Fixed combination (n = 30) [no. (%)]	Betahistine (n = 29) [no. (%)]
Very good	29 (96.7)	26 (89.7)
Good	1 (3.3)	3 (10.3)

a Patients and investigator rated treatment tolerability on a 4-point scale. There were no relevant differences between patient and investigator ratings.

marily effective on central structures, mainly the vestibular nuclei and adjacent vegetative centres in the brainstem.[19,20] Thus, both active compounds act symptomatically on structures that are involved in the pathogenesis of vertigo and vegetative symptoms. In addition, like betahistine, cinnarizine has been shown to increase blood flow in compromised intra- and extracranial areas.[16] Recently it was shown that cinnarizine directly affects calcium ion flux at calcium channels of vestibular outer hair cells.[18] Given the complex pathophysiology of vertigo, simultaneous activity at peripheral and central sites is advantageous for rapid control of vertigo of various origins. Furthermore, in vestibular disorders of otogenic origin, central symptoms frequently occur as a consequence of decompensated central stimuli integration (sensory mismatch).[7,8] Hence, a centrally acting compound may be useful in the treatment of such peripheral vestibular diseases. In fact, centrally driven vegetative symptoms such as nausea and vomiting are frequent and particularly pronounced among patients with peripheral vestibular (i.e. otogenic) vertigo,[7,8] and are therefore critical to patients' subjective well-being. In this study, the fixed combination not only effectively reduced vertigo symptoms, but also decreased concomitant vegetative symptoms to a statistically significant degree. In particular, the distressing symptoms nausea and vomiting had almost ceased after 4 weeks of therapy with the fixed combination. This effect most likely results from the antiemetic properties of dimenhydrinate, which acts centrally on the vestibular nuclei and the anatomically associated vomiting centre in the brain stem. As expected with antivertiginous drugs, neither hearing loss nor tinnitus was significantly influenced by the two study medications.

The antivertiginous effect of betahistine is thought to depend mainly on improvement of microcirculation in the inner ear.[26,27] Betahistine is primarily used in the treatment of peripheral vestibular disorders, particularly for long-term therapy of Ménière's disease.[14] The improved microcirculation leads to a reduction in vertigo and concomitant symptoms, an effect that seems to be relatively slow in onset. Thus, betahistine appears to be an appropriate treatment for long-term interval therapy rather than for the control of acute vertigo attacks, a conclusion that is reflected by the results of this study. Compared with betahistine, the effects of the fixed combination were not only significantly greater but also more rapid in onset, which might be explained by the joint actions of the two compounds within the fixed combination, i.e. the short-term effects of cinnarizine on calcium ion flux in the vestibulum and its long-term effects on cerebral vasculature, and the effects of dimenhydrinate in the brainstem.

The results of the current study show that the fixed combination of cinnarizine and dimenhydrinate is highly effective in the treatment of peripheral vestibular vertigo. These findings are consistent with those from previous studies, which demonstrated a high antivertiginous efficacy of the same fixed combination in the treatment of patients with vertigo of peripheral vestibular origin, such as Ménière's disease, vestibular neuropathy, central vestibular or the very frequently encountered vertigo of combined peripheral/central vestibular origin. In these randomised, double-blind, placebo-controlled and/or reference-controlled clinical studies, the efficacy and tolerability of the fixed combination was superior to various standard treatments, including betahistine.[21-25] Thus, the results of the current study further underline the broad efficacy of the antivertiginous fixed combination, which has previously been shown repeatedly to have superior efficacy in the treatment of vertigo of peripheral vestibular origin. The dual central and peripheral mode of action of the fixed combination represents a distinct therapeutic advantage and results in high response rates.

No serious adverse events were reported in the current study, and the vast majority of the patients in both therapy groups rated test medication tolerability as very good. Only two patients in the betahistine group reported non-serious adverse events. This demonstrates that the combination of two active compounds does not lead to a reduced tolerability but rather has a tolerability similar to that of the single compound betahistine. The high efficacy of the fixed combination together with its favourable safety profile results in a benefit/risk ratio that exceeds that of betahistine.

Conclusions

In the present study the fixed combination (consisting of cinnarizine 20mg and dimenhydrinate 40mg) proved to be a highly effective medication for the treatment of vestibular vertigo of otogenic origin. Various efficacy evaluations revealed a significantly greater relief of vertigo symptoms compared with the standard treatment betahistine. Therefore, the fixed combination may be considered a first-line treatment option for otogenic vertigo.

Acknowledgements

The conduct, statistical analysis and publication of this study were financially supported by Hennig Arzneimittel, Floersheim am Main, Germany. The authors thank Dr Andreas Iwanowitsch for the statistical analysis.

Mario Schwarz and Wolfgang Baumann are employees of Hennig Arzneimittel. The other authors have no potential conflicts of interest that are directly relevant to the contents of this manuscript.

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Correspondence and offprints: Dr *Mario Schwarz*, Department of Clinical Research, Hennig Arzneimittel, Liebigstrasse 1-2, D-65439 Floersheim am Main, Germany.
E-mail: schwarz@hennig-am.de